Preparation and Characterization of Ticagrelor Solid Self nano-emulsion

Khalid Waleed Khalid[1], Shaimaa Nazar Abd Alhammid[2]
[1]Master's degree in pharmaceutics, University of Baghdad, College of Pharmacy
[2]Ph.D Professor of Pharmaceutics, University of Baghdad, College of Pharmacy
Email: Khalid.albadri85@gmail.com

Abstract

Self nano emulsifying drug delivery system (SNEDDS) can be considered as a concentrated emulsion, containing drug that is solubilized in a mixture of oil, surfactant and co-surfactant, They administered as an oily liquid dosage form, and after mixing in the aqueous environments of the stomach they form nano emulsion. Although it is a useful method to improve solubility and bioavailability of many drugs of class II (water insoluble) and class IV (water insoluble and impermeable) drugs it have disadvantages mainly it is administered as a liquid encapsulated in soft gelatin capsules, which might be sensitive to humidity. Furthermore, the liquid preparation might cause compatibility issues with the shell of the soft gelatin capsule, so this can be avoided by solidifying the preparation to produce solid SNEDDS.

Method: After preparation of Ticagrelor a class IV drug as liquid self nano emulsion (SNE), the best solidifying agent chosen according to its loading capacity of liquid formula. Then the prepared solid formula is subjected for further test like studying the micrometric properties, disintegration time, and in-vitro dissolution studies.

Result: results showed that Avicel 102, and Aerosil 200 are the best two solidifying agent that carry the liquid formula with less amount of powder,therefore a mixture of different ratios made of these two powders. The best formula that pass all the tests was containing 90% Avicel 102 and 10% Aerosil 200.

Conclusion: combining Avicel 102 and Aerosil 200 in ratio (90 to 10) formed a solid formula of the liquid SNE with acceptable micrometric properties and dissolution rate in comparison with the marketed drug of ticagrelor (Brilinta).

Keywords: self-nano emulsion, Solid self nano emulsion, Aerosil 200, Avicel 102.

Introduction

Self-Emulsifying Drug Delivery Systems (SEDDS)

Self-emulsifying drug delivery systems (SEDDS) can be considered as a concentrated emulsion, since it contains drug, oils, surfactants and co-solvents. They administered as an oily liquid dosage form, and after mixing it in the aqueous environments of the stomach they form coarse, micro or nano size emulsion, depending on the constituents, and formulation method. Therefore, SEDDS increases the solubility of poorly water soluble drugs (1).

Address for correspondence: Khalid Waleed Khalid,
Master's degree in pharmaceutics, University of Baghdad, College of Pharmacy
Email: Khalid.albadri85@gmail.com

Access this article online	
Quick Response Code:	Website: www.pnrjournal.com
	DOI: 10.47750/pnr.2022.13.03.045

How to cite this article: Khalid Waleed Khalid, Shaimaa Nazar Abd Alhammid, Preparation and Characterization of Ticagrelor Solid Self nano-emulsion, J PHARM NEGATIVE RESULTS 2022;13:284-290.

Advantages of SNEDDS include

1. Improve the oral bioavailability enabling reduction in dose.

2. More consistent drug absorption profile.

3. Drug(s) are targeted to a specific absorption window in the GI tract.

4. Drug(s) protection from the gut's harsh environment.

5. Control of drug delivery.

6. Food effect on drug absorption can be reduced or even elimenated.

7. Increase drug loading capacity.

8. drug can be prepared in either liquid or solid dosage form (2,3).

Disadvantages of self nano-emulsifying drug delivery systems:

1-One of the obstacles for the development of SNEDDS and other lipid-based formulations is the lack of good predicative in vitro models for assessment of the formulations.

2-Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.

3-The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.

4-Volatile co-solvents in SNEDDS formulations probably will migrate to the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipid soluble drugs.

5-Formulations containing several components become more challenging to validate.

6-High production costs.

7-Low drug compatibility.

8-Drug leakage. So it may allow less drug loading (4,5).

Self nano emulsifying drug delivery system (SNEDDS) is normally a liquid preparation encapsulated in soft gelatin capsules, which might be sensitive to humidity and results in high production cost. Furthermore, the liquid preparation might cause compatibility issues with the shell of the soft gelatin capsule.

The conversion of liquid SNEDDS into solid SNEDDS provides advantages of solid SNEDDS and simultaneously eliminates the disadvantages of liquid SNEDDS, to convert liquid SNEDDS to solid SNEDDS is by adsorption onto the surface of carriers or by granulation using liquid SNEDDS as a binder. This technique is uncomplicated, cost effective, easily optimized and industrially scalable. Also can be used for heat- and moisture-sensitive molecules, thus providing an advantage over other techniques, such as spray drying and freeze drying. In addition to that various excipients utilized for the preparation of solid oral dosage forms can be employed for adsorption. The excipients should possess large surface areas to adsorb sticky and sometimes viscous oily SNEDDS formulation. Dibasic calcium phosphate, lactose, microcrystalline cellulose, colloidal silicon dioxide, aerosil, avecil, and neusilin are usual adsorbent used in the preparation of solid SNEDDS (6,7).

Advantages of solid SNEDDS

1- Liquid component in SNEDDS may interact with capsule shell , thus by solidifying the dosage form, the stability will increase and also the shelf life (8,9).

2- The solid SNEDDS can be formulated as an immediate or controlled release dosage form depending on additive powder used.

3- Solid dosage form are easier to formulate and less demand process than liquid ones.

4-The dose will be more accurate and precise in solid than liquid one (10).

5- more Patient since its solid dosage form and can be easily administered, carry and store.

6- Less production cost than liquid soft gelatin capsule.

7- Production rate is higher since higher flow ability of powder, filling the die in tablet machine will be fast (11).

8- Self-emulsifying powder can be granulated or formulate as pellet, and get the advantages that can be obtained from these dosage forms. They will eliminate the variation of the gastric emptying time, ensure easy passage in the gut and dose dumping risk will be reduce significantly. All these result in decreasing fluctuation in plasma level.

9- Many studies demonstrated that there is an equivalency in release profiles of progesterone in dogs from solid self nano-emulsifying dosage form and nano emulsion (12).

Aim of the study

The aim of the study is to solidify to solidify the liquid preparation of Ticagrelor self nano emulsion formula, to improve product stability and eliminate its interaction with capsule shell in addition to the improvement of drug solubility and bioavailability.

Materials & Method

Materials

The following materials were purchased from

Ticagrelor, Aerosil 200 and Avicel 102 (hyper chemical china), oleic acid, , tween 20, tween 80 (Solvochem UK), propylene glycol (Gain land chemical community. UK). mannitol, starch® 1500, avicel PH101, dibasic calcium phosphate, Carboxy methyl cellulose (Thomas baker India).

Method

Preparation of Ticagrelor Liquid Self-nanoemulsion Formula

The liquid formula was prepared first to be solidify, an optimum formula was chosen in a previous study. Each prepared single dosage form contains 0.05 gram oleic acid as oil, 0.36 gram tween 20 as surfactant, 0.09 gram Propylene glycol as co surfactant, 0.09 gram ticagrelor the drug.

Oleic acid, tween 20 and propylene glycol were mixed in vortex mixer before adding drug for about 3 min to ensure homogeneity, then accurately weighted ticagrelor was added to the(oil, surfactant, and co surfactant) mixture, with continuous stirring in vortex mixer until solid dispersed in oil/Smix mixture, the mixture was transferred to the sonicator until all drug dissolved (13).

Selection of Proper Solid Adsorbent

The selected formula of ticagrelor self-nanoemulsion formula was solidified using different porous hydrophilic or hydrophobic adsorbents including mannitol, starch® 1500, avicel PH101, avicel PH 102, dibasic calcium phosphate, Carboxy methyl cellulose, and aerosil 200.Levigation method was used to determine the liquid loading capacity or adsorbing capacity of each adsorbent; adsorption capacity is the amount in a gram of liquid formula that adsorbed by one gram of solid carrier (14).

1 gram of solidification powder is placed in the mortar, then the formula was added gradually to the mortar and blended with pestle and check for flowability. After that, the two best adsorbent with higher loading capacity are selected and subjected for further tests (15).

Evaluation of Ticagrelor Solid SNE

The powder characteristics in term of flowability must be checked before filling into hard gelatin capsules, since inadequate flowability of the powder will affect uniformity of blending negatively, and this results in an inaccurate filling and dosing. The conventional laboratory methods for flow property assessment are the following:

Micromeritic Properties

Bulk and tapped density

The bulk and tap density of powdered TCG SNE was determined by measuring the volume of the powder before and after tapping. A determined quantity of powder is placed in 10 ml graduated cylinder a the volume before tapping was recorded, then after several taps until no change in volume occurred. the formed volume is reordered and the densities calculated using the following equations (16):

$$\rho_b = \frac{M_s}{V_{bt}}$$

$$\rho_t = \frac{M_s}{V_{at}}.$$

were Pb is the bulk density, Ms is the mass of powder, Vbt is the bulk volume

and Pt is the tapped density, Vt is tapped volume

Angle of repose (θ):

The highest angle achievable between the surface of a pile of powder and the horizontal plane is defined as angle of repose. The angle of repose can be used to calculate the frictional force in a loose powder or grains. It's a measure of the powder's flow characteristics (17).

$\tan \theta = H / R$

Where, θ = angle of repose

H = pile height

R = radius of the base of pile

The powder combination was allowed to flow through a funnel that was mounted on a stand at a specific height (H). After that, the angle of repose was estimated by measuring the height and radius of the powder heap that had developed. The powder particles were carefully slide and rolled over each other through the funnel's sides.

Relationship between powder flow property and the angle of repose is shown in table (1) (18).

Table (1): Relationship Between Angle of Repose and Powder Flow Property (18)

Angle of repose degree	Type of flow
< 20	Excellent
20-30	Good
30-34	Passable
>40	Very poor

Flow Rate:

The rate at which a certain mass emerges from the end of a funnel with sufficient diameter has been characterized as the flow rate of a powder.

The flow rate of each formulation's granules was established by pouring precisely weighed quantities of granules into a funnel with an 8 mm diameter aperture. A stopwatch was used to record the time it took for the entire granule mass to emerge from the aperture. The flow rate was determined using the equation below (19):

$$\textbf{Flow Rate} = \frac{\textbf{Weight of granules}}{\textbf{Time in seconds}}$$

Carr's Index

Carr devised an indirect method of determining powder flow from bulk densities. The % compressibility of a powder was a direct indicator of the possible strength and stability of a powder arch or bridge. Each formulation's Carr's index was computed using the equation below, and the result explanation is shown in table (10) (20).

Compressibility index (%) = [(ρt –ρb)/ρt)] × 100

Table (2): Carr's Index as an Indication of Powder Flow (20)

Carr's index (%)	Type of flow
=10	excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
38 and over	Very very poor

Characterization of Solid SNEDDS

Drug Content

Drug content measurement for solid SNE is very important test to ensure the right distribution of liquid formula in solid carrier.

10 capsules content were dispersed in 10 ml of ethyl acetate, then after continuous shaking and sonication for about 15 min, the samples were centrifuged at 3500 rpm for about 15 min, then the supernatant was separated and diluted or assay spectrophotmetrically for drug content (21).

Determination of Disintegration Time of Solid SNE Capsules

One capsule was placed in each basket in a disintegration apparatus (totally 6 capsules), the disintegration media used was 0.1 N HCl and the temperature was maintained at 370 ± 20. The disintegration time was recorded after the capsule powder content passed through the basket mesh and may only the hard gelatin shell remnant stays (22).

In-Vitro Dissolution of The Prepared Solid Self-Nanoemulsion Capsule

The dissolution of the prepared formulas of solid SNE was determined using dissolution apparatus 2, in which one capsule is placed in a basket and attached to a paddle. In each beaker a 900 ml of dissolution media 0.1 HCl containing 1% tween 80 to maintains sink condition. Then the temperature maintained at 37 ± 20 with a rotating speed of 100 rpm at fixed time intervals (5,10,20,30,40) 5 ml of sample were withdrawn and replaced with fresh 5 ml of same dissolution media to maintains sink condition. The withdrawn samples were filtered through 0.45 μm filter. Ticagrelor concentration in the filtrate was analyzed. Dissolution of pure Ticagrelor powder was also done (23).

Results

Preparation of Ticagrelor Liquid Self-nanoemulsion Formula

The liquid formula was prepared and showed a good consistency and clarity, all the drug was dissolved in the oil, surfactant mixutre, with no precipitation seen, this formula is ready to be solidify.

Selection of Proper Solid Adsorbent

The selection of the proper powder for the solidification was based on two parameters, the flowability and the adsorption capacity. With the aim to prepare self-nano emulsifying powders using as little solid carrier as possible to

enable development of solid SNEDDS with the highest drug loading (24), screening of porous solid carriers for their adsorption of SNEDDS capacity was performed and the following results obtained.

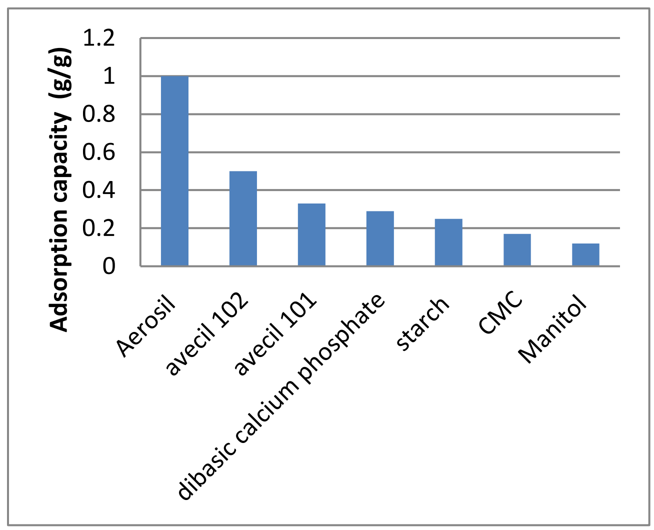

Figure (1): Maximum adsorption capacity of one gram of different carriers for liquid SNEDDS

Aerosil 200 and avicel 102 shows the highest adsorption capacity, although the high difference in the adsorption capacity between the two carriers, but the relative higher density of Avecil 102 in comparison to Aerosil 200 made the final volume solid SNE formula with equal amount of liquid SNE formula relatively equal and capable of filling a capsule with same drug content (45 mg of ticagrelor).

Therefore 11 formulas of solid ticagrelor self nano-emulsion were prepared, by combining two carriers in different ratios or alone, to determine the best formula in respect of micrometric parameters and drug release.

Table (3): Solid Ticagrelor -SNEDDS Different Constituents

	Avicel 102 %	Aerosil 200 %
F1S	100	0
F2S	90	10
F3S	80	20
F4S	70	30
F5S	60	40
F6S	50	50
F7S	40	60
F8S	30	70
F9S	20	80
F10S	10	90
F11S	0	100

Characterization of Solid SNEDDS

Micromeritic Properties

Studying the micrometric properties of the prepared powder is important to determine flowability of prepared formulas and suitability to fill in hard gelatin capsule. The micrometric properties of prepared formulas are shown in table (4).

Table (4): Micrometric Properties of Prepared Ticagrelor-SSNE Formula

	Angle of repose	Flow rate (gram/sec)	Carr's Index	Hausner ratio
F1S	32	19	20	1.25
F2S	30	21	19.1	1.20
F3S	28	21	17.9	1.192
F4S	27	22	17.1	1.175
F5S	26	22.1	16.6	1.163
F6S	25	22.5	15.9	1.155
F7S	23	22.9	15.1	1.142
F8S	22	23.4	14.2	1.139
F9S	21	24	13.7	1.122
F10S	20	24.2	12.9	1.113
F11S	19	25	12	1.10

From the obtained results, it seems that all formulas are in the accepted range and show good powder flowability, although as the content of avicel decrease and the content of aerosil increase, the powder show better flow properties , this is due to the small particle size of aerosil 200 in addition to its lower density and surface area (200 m2/g) (25).

Drug Content

Drug content in all formulas ranged from 98.4 to 99.6 as shown in table (5). This result is within the stated range for drug content in USP, and indicating that all the drug was successfully adsorbed by the carrier with uniform distribution within the solid carrier.

Disintegration Time of Solid SNE Capsules

The disintegration time for all prepared capsules ranged from 1 minute to 1.25 minute, with no significant difference found among tested formulations ($p > 0.05$).

This fast disintegration time may be due to porosity and rapid absorption of water by avicel 102 and the porosity and hydrophilicity of aerosil 200 (26,27).

Table (5): Drug Content and Disintegration Time of Prepared TCG-SSNE Formulation

	Drug content %	Disintegration time
F1S	99	1 min
F2S	99	1.03 min
F3S	98.4	1.08
F4S	98.6	1.11
F5S	99.1	1.12
F6S	99.6	1.13
F7S	98.9	1.15
F8S	99	1.17
F9S	98.6	1.20
F10S	99.5	1.22
F11S	99.1	1.25

Formulas that contain higher amount of avicel showed faster disintegration than other formulas with lower avicel content, this is may be due to the swellability and insolubility of avicel. Thus, the disintegration media can quickly be drawn up or wicked up by the capillary action of porous fibrous structure, resulting in swelling and rupturing the inter-particulate bonds of the solid powder (28).

In-vitro Dissolution of the Prepared Solid Self-nanoemulsion Capsule

The release profile of solid formulation is shown in table (6) , and the release of the best formula in comparison to the marketed Brilinta is shown in figure (2), F2S was chosen as the best formula depending on the obtained overall test results, although the release profile of F1S is slightly better than that of F2S, but there was no significant difference between them, and the flowability of F2S powder is more reliable than that of F1S.

Table (6): The Release of Drug from the Prepared Capsules of Ticagrelor-SSNE

	F1S	F2S	F3S	F4S	F5S	F6S	F7S	F8S	F9S	F10S	F11S	Brilinta
5	5	4.8	4.6	4.2	4	3.8	3.3	2.9	2.7	2.5	2.5	30
10	60	59	55	54	50	46	44	40	38	35	32	47
20	85	85	80	80	76	71	70	69	69	64	61	71
30	100	100	98	98	94	89	88	84	81	78	77	90
40	100	100	100	100	100	100	100	98	96	85	80	100
50	100	100	100	100	100	100	100	100	100	95	89	100
60	100	100	100	100	100	100	100	100	100	100	100	100

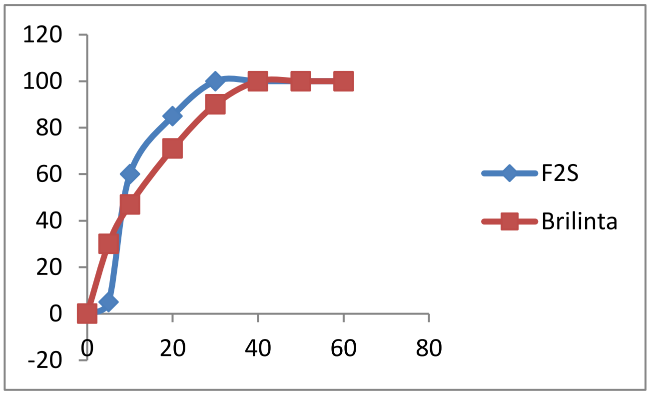

Figure (2): Release of drug from F2S and marketed TCG tablet (Brilinta®)

By comparing F2S with marketed Brilinta, a rapid release from the marketed tablet is noticed with a relative delay from formulated capsule, this is due to the type of dosage form, in which marketed tablet disintegrates rapidly and release drug while formula F2S needs time for capsule shell to dissolve and release its content, after the capsule shell have been dissolved, a faster release is seen from F2S formula and full release of its content within 30 minutes, while it takes 40 minutes for the marketed Ticagrelor (Brilinta®) to full release.

References

1. Balakrishnan P, Lee BJ, Oh DH, et al. Enhanced oral bioavailability of dexibuprofen by a novel solid self-emulsifying drug delivery system (SEDDS). Eur J Pharm Biopharm. 2009; 72(3):539-545.
2. Cho H, Kang JH, Ngo L, Tran P, & Lee YB. Preparation and Evaluation of Solid-Self-Emulsifying Drug Delivery System Containing Paclitaxel for Lymphatic Delivery. Journal of Nanomaterials. 2016; 2(4):1–14.
3. Patel PA, Chaulang GM, Akolkotkar A. Self Emulsifying Drug delivery system: A Review. Research Journal of Pharmarmaceutics and Technology, 2008; 1:313-323.
4. Khedekar K, Mittal S. Self Emulsifying Drug Delivery System: A Review. Int J Pharm Sci Res. 2013; 4(12):4494-07.
5. An Y, Yan X, Li B, Li Y. Microencapsulation of capsanthin by self-emulsifying nanoemulsions and stability evaluation. European Food Research and Technology.2014; 239(6):1077–1085.
6. Basit AW, Newton JM. Formulation of ranitidine pellets by extrusion-spheronization with little or no microcrystalline cellulose. Pharm. Dev. Technol. 1999; 4:499–505.
7. Okada S, Nakahara H. Adsorption of drugs on microcrystalline cellulose suspended in aqueous solutions. Chem. Pharm. Bull. 1987; 35:761–768.
8. Cole ET, Cadé D, Benameur H. Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. Adv. Drug Deliv. Rev. 2008; 60:747–756.
9. Ma H, Chu M, Itagaki K, Xin P. Formulation and In Vitro Characterization of a Novel Solid Lipid-Based Drug Delivery System. Chem. Pharm. Bull. 2014; 62:1173–1179.
10. Tang B, Cheng Jian G, Gu C. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discovery Today. 2008; 13:606-612.
11. Rao BP, Baby B, Durgaprasad Y, Rames K. Formulation and evaluation of SME;DDS with Capmul MCM for enhanced dissolution rate of valsartan. RGUHS J. Pharm. Sci. 2013; 3:33–40.
12. Abuhelwa YA, Foster JRD, Upton NR. A Quantitative Review and Meta-models of the Variability and Factors Affecting Oral Drug Absorption—Part II: Gastrointestinal Transit Time. AAPS Journal. 2016; 18(5):1322-1333.
13. Ravindra N, Piyush P, Kumar A. Self-Nano-Emulsifying Drug Delivery System: In Vitro and In Vivo Evaluation. AAPS PharmSciTech.2016; 17:1240–1247.
14. Katla VM, Veerabrahma K. Cationic solid self-micro emulsifying drug delivery system (SSMED) of losartan: Formulation development, characterization and in vivo evaluation. J Drug Deliv Sci Technol. 2016; 35:190-9.
15. Bolko K, Ilic IG, Gasperlin M, Zvonar Pobirk A. Self-Microemulsifying tablets prepared by direct compression for improved Resveratrol delivery. Int J Pharm. 2018; 548(1):263-75.
16. Ahmad MZ, Akhter S, Anwar M, Rahman M. Compactibility and compressibility studies of Assam Bora rice starch, Powder Technol. 2012; 14(2):281–286.
17. Maurya SD, Tilak VK, Dhakar RC, Verma KK, Soni U. Preparation and evaluation of floating tablet of Famotidine through solid dispersion. International Journal of Current Research and Review. 2011; (2)1:21-30.
18. Thoke SB, Sharma y, Nangude R. Formulation development & evaluation of effervescent tablet of Alendronate sodium with vitamin D3. Journal of Drug Delivery & Therapeutics. 2013; 3(5):65-74.
19. Salim P, Siddaiah M. Formulation and evaluation of effervescent tablets: a review. Journal of drug delivery and therapeutics. 2018; 8(6):296-303.
20. Gawali Vikas B, Mahesh B, Dalvi B, Tarkasband S. Development and evaluation of Polyhebral powder formulation as energy booster. Journal of Pharmacognosy and Phytochemistry. 2018; 7(3):1576-1580.
21. Pravala K, Nagabandi VK, Divya A. Enhancement of bioavailability of Nebivolol hydrochloride through liquisolid formulations: In vitro and in vivo evaluation. Der Pharmacia Lett. 2013; 5(6):151-163.
22. Archer M, Kumadoha D, Yeboaha GN. Formulation and evaluation of capsules containing extracts of Cassia sieberiana for improved therapeutic outcome. Scientific African, 2020;10: 234-242.
23. Sabri LA, Hussien AA. Formulation and In-Vitro Characterization of Solidified Nebivolol Self-Nanoemulsion using Liquisolid Technique.Sys Rev Pharm. 2020; 11(3): 261 268.
24. Shanmugam S, Baskaran R, Balakrishnan P, Thapa P, Yong CH, Yoo BK. Solid self-nanoemulsifying drug delivery system (S-SNEDDS) containing phosphatidylcholine for enhanced bioavailability of highly lipophilic bioactive carotenoid lutein. European Journal of Pharmaceutics and Biopharmaceutics. 2011; 79(2):250-257.
25. Mardiyanto M, Untari B, Anjani R, Fithri NA. Solid self nano emulsifying drug delivery system (Solid SNEDDS) of mefenamic acid: formula optimization using aerosil 200 and avicel PH-101 with factorial design. International research journal of pharmacy. 2020; 11(2):234-242.

26. Chaerunisaa AY , Sriwidodo S, Abdassah M. Microcrystalline Cellulose as Pharmaceutical Excipient. In: Ahmad U, Akhtar J, editors. Pharmaceutical Formulation Design - Recent Practices
27. Hentzschel CM, Alnaief M, Smirnova I. Tableting properties of silica aerogel and other silicates. Drug Development and Industrial Pharmacy. 2012; 38(4):462–467.
28. Sabri LA, Hussien AA. Formulation and In-Vitro Characterization of Solidified Nebivolol Self-Nanoemulsion using Liquisolid Technique.Sys Rev Pharm. 2020; 11(3): 261 268.